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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,200	11/18/2003	Manne Satyanarayana Reddy	BULK 3.0-032	4125

45776 7590 05/10/2007

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EXAMINER	
MORRIS, PATRICIA L	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
05/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,200	REDDY ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-17 and 19-34* is/are pending in the application.

4a) Of the above claim(s) *19-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-17,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-9, 11-17, 33 and 34 are under consideration in this application.

Claims 19-32 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Election/Restrictions

The restriction requirement is deemed sound and proper and is hereby made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-9, 11-17, 33 and 34 are rejected under 35 U.S.C. 102(a) and/or (e) as being anticpated by Cotton et al. for the reasons set forth in the previous Office action.

Again, Cotton et al. specifically disclose the instant compound. Note, example 1, therein. Also, note column 2, line 47-50, wherein it is recited that magnesium S-omeprazole hydrates are highly crystalline. Hence, the instant compound is deemed anticipated therefrom.

Applicants argue that they have provided X-ray diffraction data that clearly demonstrates that the instant trihydrate and the recited compositions in claims 6-9 and

11-16are distinctly different. Applicants have failed to show a **side-by-side-comparision.**

X-ray diffraction pattern **alone** does not demarcate the identity of two products. It is well recognized in the crystalline solid art that sometimes the difference in X-ray diffraction pattern is very minor and and must be carefully evaluated before a definitive conclusion is reached. See US Pharmacopia of record. Further, Davidovich et al. on page 16, states that changes in powder X-ray diffraction often resulted from experimental artifacts rather than polymorphism and that most of these changes were due to particle size/morphology, sample holder/preparation and instrument geometry. Note figure 4.21 on page 118 of Bernstein wherein the same compound shows two different X-ray patterns. Page 272 of Bernstein shows that two identical X-ray patterns, but one is the chemical compound pigment Yellow 14, wherein R is CH_3, while the other is the pigment Yellow 63, R is Cl. Thus, this is an example of identical X-ray displayed by different compounds. The figure on page 273 showed two X-ray diffraction patterns collected on crystals and recrystals after melting. Although, there are new peaks, the authors concluded that "it may not be a pure medication", *i.e.*,not a true polymorph. Caira recites several cases of "vanishing" polymorphs. Note page 165 therein.

The newly added references are supplied to as state-of-the-art evidence rebutting applicants' arguments in the instant response.

Claim Rejections - 35 USC ∋ 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9, 11-17, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cotton et al. in view of Bohlin et al., Lindberg et al., Haleblian et al., Muzaffar et al., Chemical & Engineering News, US Pharmacopia, Brittain et al and Concise Encyclopedia Chemistry for the reasons set forth in the previous Office action.

Again, Cotton et al, teach the crystalline form of the magnesium salt of s-omeprazole trihydrate. Note example 1 therein. Bohlin et al. and Lindberg et al. teach that s-omeprazole and its salts can exist in different crystalline states. Muzaffar et al., Brittain et al. and Haleblian et al. teach that compounds can exist in amorphous forms as well as in crystalline forms. Note, for example, column 1, lines 58-63, of Bohlin et al. or

page 60 of Muzaffar et al. Chemical & Engineering News, US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different crystalline forms. No unexpected or unobvious properties are noted.

Contra to applicants' assertions in the instant response, one having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. It is well recognized in the pharmaceutical field that many solids exhibit polymorphism which is the innate nature of the particular drug. (see US Pharmacopia, Brittain pages 178-179,219 or page 33 of Chemical Engineering News). It is also well recognized in the art that the different polymorphs will display different physical properties such as X-ray diffraction, melting point, etc. (see page 911 of Haleblian or page 33 of Chemical Engineering News). As clearly stated by Brittain (p.1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268, ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant compounds are drawn to the ***same pure substance*** as the prior art that only have *different arrangements and/or different conformations of the molecule.* A mere difference in physical property is a well known conventional variation for the same pure substance is prima facie obvious (see the references of record, for example, Brittain et al, pages 1-2). The instant

compounds are not new as asserted by applicants. Hydrates are identical crystalline forms.

Again, applicants do not point to any objective evidence which demonstrates that the claimed polymorphs and polymorphis compositions exhibit any properties which are actually different from the closest prior compounds embraced by Muller et al. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977); In re Hoch, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970). Allegations by counsel do not take the place of **any objective evidence.** Applicants merely assert that the X-ray diffraction patterns are different. The mere difference in a physical parameters such as X-ray diffraction pattern does not offer any unexpected advantage of the instant hydrate *vis-à-vis* the prior art hydrate. Further, applicants have failed to show that the instant compound *vis-à-vis* the prior art compound shows any unexpected or superior properties in reducing gastric secretion.

Applicants merely allege that the cited Brittain passage supports their assertion the USPTO routinely issues patents directed to new polymorphs. However, **applicants' allegations fail to show that the instant hydrate as any advantage at all over the prior art hydrate.**

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Again, there is a lack of description as to whether the compositions are able to maintain the compound in the crystalline form claimed. Processing a compound into a pharmaceutical composition could create a different form than the crystalline form being claimed or even back to the compound itself. See pages 912-913 of Habeblian. Doelker et al. Abstract and English translation of the French article is now provided, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or dosage form." Taday et al. p 831...Once in the desired crystalline form, the polymorphic form may be changed by incorrect storage or even during tablet preparation" and p. 836, figure 8, wherein the compound form four in the pharmaceutical composition resulted in similar spectra. The specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. The X-ray diffraction and Infrared spectrum data in the specification only pertains to the magnesium hydrate rather than the compositions being claimed.

Contra to applicants' arguments in the instant brief, applicants have **failed to provide any objective evidence that the instant polymorphs are indeed maintained in the compositions.** Chemical & Engineering News disclose that formulation of drugs or pharmaceuticals in its metastable forms, for example, on polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. Muzaffar et al., p. 60 states "At any one temperature and

pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form." And p. 63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism.

The specification lacks description of how the pharmaceutical compositions can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Otsuka et al., p. 852 "..in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process." Disclosure of X-ray diffraction patterns for pharmaceutical compositions comprising the crystalline forms are lacking in the specification. The X-ray diffraction patterns in figure 1 and infrared spectra only supports the crystalline form of magnesium esomperazole trihydrate.

Applicants' assertions and allegations in the instant response do not take the place of objective evidence. Applicants have failed to show that the polymorph in the composition will maintain its form after pharmaceutical formulation. Applicants have provided no objective evidence that the instant polymorphs will not be identical to prior art compound because *"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"* (see Jain p.316). It is well known that the compound will become amorphous in solution. (see Ulicky) It is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a particular crystalline

form, no predictability can be found that such forms will prevail in pharmaceutical compositions. See Chemical & Engineering News.

Further, the specification has also not described how all the crystalline forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment of disorders associated therewith with gastric acid secretion. In addition, it is well recognized in the art that the compound is given to the subject in a physicological environment, *i.e.,* administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical and biological activity results from the particular form instead of the solution state of the compound.

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

Contra to applicants' allegations in the instant response, hydrates may dehydrate. Hydrates tend to convert from less stable to more stable forms (see Brittain et al., page 200). Phase changes due to hydration/dehydration of pharmaceutical compounds during processing or in the final product may result in an unstable system that would effect the bioavailability of drug from solid dosage forms.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business

Center (EBC) at 866-217-9197 (toll-free).

Patricia L. Morris
Primary Examiner
Art Unit 1625

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May 7, 2007